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EDITORIALS

Pioglitazone and the risk of bladder cancer

Risks seem to outweigh benefits as yet more evidence emerges

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Therapeutic strategies must be chosen with an accurate and updated assessment of both expected benefits and potential risks to sustain the confidence of patients and guarantee safety. In a linked study (doi:10.1136/bmj.e3645), Azoulay and colleagues found that more than two years daily exposure to pioglitazone doubled the risk of bladder cancer.[1] They also found an association between bladder cancer and both the dose and the duration of pioglitazone treatment.[1] This nested case-control study benefits from the use of data from the large high quality General Practice Research Database. A new user design was used for the first time to study this particular risk. Strengths of the study also include adjustment for many confounders, the matching of case and controls on duration of follow-up, and comparison with the incidence of bladder cancer in patients exposed to rosiglitazone. These allowed the study's authors to draw reliable conclusions with a minimal risk of indication bias due to severity of diabetes.

Much is known that places the current findings in context. Firstly, it has recently been shown that pioglitazone has a pharmacological profile comparable to that of the glitazar compounds.[2] These dual α and γ peroxisome proliferator activated receptor agonists were developed to improve both glucose and lipid metabolic parameters but were rapidly withdrawn mainly on the grounds of carcinogenic effects in animals.

Secondly, before marketing authorisation (1999 in the United States, 2000 in Europe), preclinical data on pioglitazone reported the occurrence of bladder cancers in male rats.[3] These data were added to the pioglitazone Summary of Product Characteristics without specific information for prescribers, particularly recommendations for patient selection and monitoring. That the risk of bladder cancer might be comparable in humans was rejected by a mechanistic hypothesis that involved pioglitazone induced urolithiasis leading to chronic irritation of the bladder in rats. Surprisingly, urine analysis data from clinical trials were not extensively investigated. Later, in 2011, experimental work showed that although an acid forming diet reduced both the number of calculi and bladder cancers in male rats, the diet did not reduce the incidence of hyperplasia.[4]

Thirdly, in the 2005 report of the PROactive randomised clinical trial, which compared pioglitazone with placebo, the number of true bladder cancers was not correctly counted in the placebo arm, which masked the difference between groups.[5]

Fourthly, additional information from postmarketing observational studies suggests a positive association between chronic exposure to pioglitazone and bladder cancer. These studies included one study of the US Food and Drug Administration (FDA) Adverse Event Reporting System (reporting odds ratio 4.30, 95% confidence interval 2.82 to 6.52)[6]; one interim analysis of the US Kaiser Permanente Northern California prospective cohort (exposure >2 years: hazard ratio 1.4, 1.03 to 2.0),[7] which resulted in an FDA warning on September 2010[8]; and one retrospective cohort from the French health insurance database (overall hazard ratio 1.22, 1.05 to 1.43; exposure >2 years 1.34, 1.04 to 1.79),[9] which led to the suspension of pioglitazone in France in June 2011.[10] Since then, two retrospective cohorts using the Taiwanese reimbursement database failed to show any significant association: one may have lacked statistical power,[11] and the other could not exclude a potential increased risk for exposure greater than three years (odds ratio 1.56, 0.51 to 4.74).[12]

Lastly, on 20 December 2011, the last version of the Summary of Product Characteristics for pioglitazone showed that, in a meta-analysis of randomised clinical trials, cases of bladder cancer were reported more often with pioglitazone (19 cases in 12 506 patients; 0.15%) than in control groups (seven cases in 10 212 patients; 0.07%), with a hazard ratio of 2.64 (1.11 to 6.31; P=0.029).[3]

Since then, the European Medicines Agency stated that pioglitazone is contraindicated in patients with current bladder cancer, a history of bladder cancer, or uninvestigated macroscopic haematuria, and that risk factors for bladder cancer should be assessed before starting pioglitazone treatment. Patients are advised to report macroscopic haematuria or other urinary symptoms promptly.[13] These criteria may not be sufficient to avoid the exposure of patients at risk and to properly monitor treated patients.

Taking into account Azoulay and colleagues' current findings and given the consistency of these results, the relative strength of the association, the dose-response effect, the known pharmacodynamic characteristics of pioglitazone, and evidence of a significant association in a meta-analysis of randomised

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trials, it can confidently be assumed that pioglitazone increases the risk of bladder cancer. It also seems that this association could have been predicted earlier. Worldwide, exposure to pioglitazone is estimated to be more than 20 million patient years.[13] Considering that the benefit of pioglitazone in reducing cardiovascular events is questionable, prescribers who are ultimately responsible for therapeutic choices can legitimately question whether the benefit-risk ratio of pioglitazone is still acceptable for their patients with diabetes.

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1 Azoulay L, Yin H, Filion KB, Assayag J, Majdan A, Pollak MN, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ* 2012;344:e3645.
2 Hillaire-Buys D, Faillie JL, Montastruc JL, Petit P. Stay vigilant: a glitazone (pioglitazone) can hide a glitazar! *Eur J Clin Pharmacol* [forthcoming].
3 Actos. Product information as approved by the CHMP on 20 October 2011, pending endorsement by the European Commission (updated 20 December 2011). www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500109185.pdf.
4 Sato K, Awasaki Y, Kandori H, Tanakamaru ZY, Nagai H, Baron D, et al. Suppressive effects of acid-forming diet against the tumorigenic potential of pioglitazone hydrochloride in the urinary bladder of male rats. *Toxicol Appl Pharmacol* 2011;251:234-44.
5 Hillaire-Buys D, Faillie JL, Montastruc JL. Pioglitazone and bladder cancer. *Lancet* 2011;378:1543-4; author reply 4-5.
6 Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care* 2011;34:1369-71.
7 Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, et al. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 2011;34:916-22.
8 Food and Drug Administration. Drug safety communication: ongoing safety review of Actos (pioglitazone) and potential increased risk of bladder cancer after two years exposure. www.fda.gov/%20Drugs/DrugSafety/ucm226214.htm.
9 Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia* 2012; published online March 31.
10 AFSSAPS. Use of medications containing pioglitazone (Actos, Competact) suspended. 2011. www.ansm.sante.fr/var/ansm_site/storage/original/application/4e293bcd0814c025b94d46d7502a0958.pdf.
11 Tseng CH. Pioglitazone and bladder cancer: a population-based study of Taiwanese. *Diabetes Care* 2012;35:278-80.
12 Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, Arnold Chan K. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. *Hepatology* 2012;55:1462-72.
13 European Medicines Agency. Assessment report for Actos, Glustin, Competact, Glubrava, Tandemact. 2011. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000285/WC500126656.pdf.

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